SUPPORT FOR THE AMENDMENTS

Claims 40 and 41 have been added.

Support for new Claims 40 and 41 is provided by the specification as originally filed, for example, at page 1, lines 5-30, page 3, lines 22-24, page 4, lines 4-8, and page 7, lines 11-16.

No new matter has been presented by this amendment.

REMARKS

Claims 1-41 are pending in the present application.

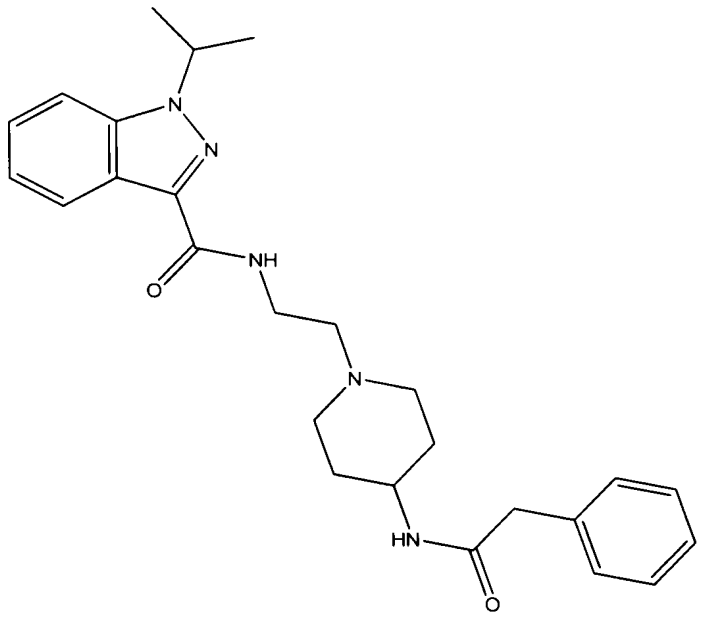
The rejection of Claims 1-35 under 35 U.S.C. 103(a) over Catlow et al (US 5,654,320) in view of Suzuki et al (US 6,096,746) and Schaus et al (J. Med. Chem. 1998) is respectfully traversed.

In the Office Action mailed January 16, 2009, the Examiner alleges that "it is erroneous for applicant to misinterpret the references that the compounds were active only in treating gastrointestinal disorder. Further, the Examiner also asserts that the previous office action clearly delineated that the references are indazolyl-piperidinyl compounds which have "5HT4" receptor modulating activity." Applicants respectfully submit that the previous response simply reflected the Examiner's actual statement in the previous Office Action that "Catlow et al... disclosed 5HT4 receptor binding components for treating gastrointestinal disorder..." (see page 3, second paragraph of the Office Action mailed August 4, 2008). Nowhere in the previous Office Action was it suggested that Catlow et al's compounds or the compounds in the other references are useful as an analgesic for the treatment of pain, much less chronic pain, including rheumatoid arthritis, osteoarthritis, fibromyalgia, oncology pain, and neuropathic pain (see page 7, lines 11-16).

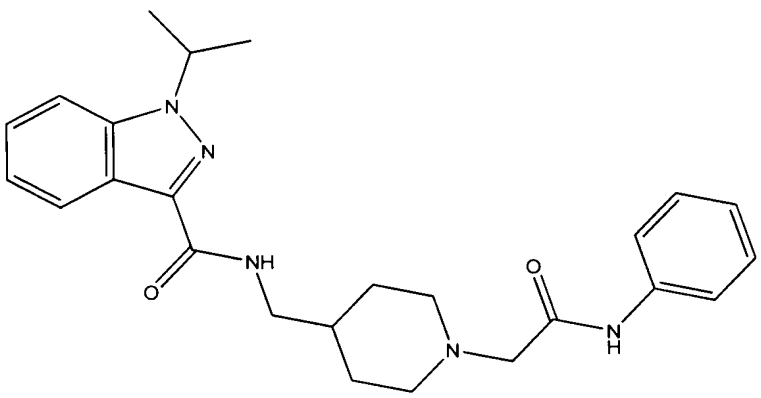
Indeed, it is only now that the Examiner attempts to give Catlow et al a generic and speculative application by picking a choosing a single line (column 19, line 21) despite no reasonable basis to conclude that the reference is useful within the scope presented. Indeed, the Examiner now points to that paragraph at column 19, lines 17-32 of Catlow et al to allege that this reference does disclose a use for treating pain. Be that as it may, this disclosure by Catlow et al seems to equate the compounds disclosed therein to a snake oil that is effective for treating and/or preventing virtually any disorder. Clearly this disclosure is insufficient to

establish that the compounds disclosed by Catlow et al would be effective for treating pain, much less that compounds modified in the manner necessary to arrive at the claimed invention would have such an activity.

Catlow et al is cited as disclosing 5-HT4 receptor binding compounds for treating gastrointestinal disorder and specifically referred to the compound of column 14, Example 26. Example 26 of Catlow et al, N-[2-(4-benzylcarbonylamino-1-piperidinyl)ethyl]-1-(2-propyl)-1H-indazole- 3-carboxamide, has the formula:



The Examiner alleges that the compound of Example 26 of Catlow et al is "structurally very close to the claims" citing the speices of Claim 8, N3-((1-(2-Oxo-2-(phenylamino)ethyl)-4-piperidyl)methyl)-1-(1-methylethyl)-1H-indazole-3-carboxamide, which has the formula:



The Examiner then alleges that the compound of Claim 8 only differs from the compound of Example 26 of Catlow et al by (i) one methylene linker between the indazolyl and the piperidinyl ring, (ii) the rotation of the piperidinyl ring, and (iii) the reverse amidomethyl linkage.

The Examiner has alleged that the substitutions on the phenyl ring are *prima facie* obvious in view of Schaus et al at page 1944. However, on page 1944 only compounds 2 cisapride and 7, RS100235 have substitutions on the phenyl ring. However, these compounds are structurally different from the compounds of the present invention, in particular RS100235, and on page 1943, right column, last paragraph it is stated that cisapride is not particularly potent for 5-HT4 receptors and has high affinity for other receptors. So, even if substitution of a phenyl ring are well known to the skilled artisan, there is no suggestion in Schaus et al to provide such substitutions.

Applicants once again direct the Examiner to *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) in which the Court of Appeals for the Federal Circuit clearly state that in order to find a *prima facie* case of unpatentability, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required (*Takeda* at 1174, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d

688, 16 USPQ2d 1897 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

Moreover, as clearly stated by *Takeda* at 1174, the Court squarely addressed the test for *prima facie* obviousness enunciated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385](2007) in the context of chemical compounds:

> That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*** (*emphasis added*)

In the Office Action mailed August 4, 2008 and reiterated in the Office Action mailed January 16, 2009, the Examiner alleges that the artisan would have been able to modify the disclosed compound in Example 26 of Catlow et al based on the disclosures of Suzuki et al and Schaus et al. Applicants disagree with this allegation and maintain that neither Suzuki et al nor Schaus et al provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds.

However, the Examiner maintains that:

- difference (i) is an optional choice for such compounds in view of Suzuki et al., column 54-55 examples 18 and 19,

- difference (ii) is an optional choice for the class of 5HT4 receptor binding in view of Schaus et al., page 1948 table 3 vs. page 1950 table 5, and
- difference (iii) is an optional choice for such compounds in view of Schaus et al., page 1948 compound 19j vs. page 1950 compound 23j, both having potent binding activity as stated on page 1948 right column last four lines and page 1951 right column 2nd paragraph last 10 lines.

Applicants disagree with these allegations by the Examiner and the ultimate allegation of obviousness.

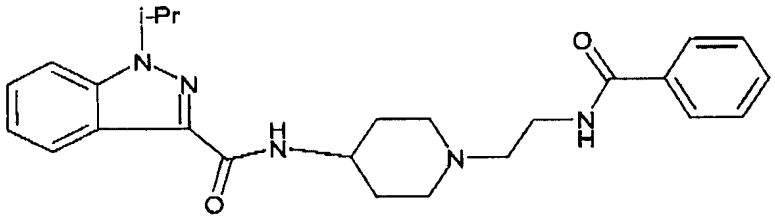
With respect to difference (i) Suzuki et al do *not* disclose or suggest that the difference of a methylene linker is an optional choice. When comparing homologous compounds 23, 18 and 19 of Table 1 at column 64 (having 0, 1, or 2 methylene groups as linker between the amido group and the piperidinyl ring) there is a clear indication that the higher activity (A) is connected with m=2 (compound 19, A=5.89), followed by m=0 (compound 23, A=5.55) and last by m=1 (compound 18, A=5.10). On the contrary, when comparing homologous compounds 22, 7, and 8 (also having 0, 1, or 2 methylene groups as linker between the amido group and the piperidinyl ring) the higher activity is connected with m=1 (compound 7, A=5.30), followed by m=0 (compound 22, A=5.16) and last m=2 (compound 8, A=4,97). So, this confirms what is the actual knowledge of the skilled artisan in pharmaceutical chemistry, that is that a simple change can have different effect depending from the actual and specific molecular structure under consideration.

Notably, the Examiner does not address the foregoing argument with respect to difference (i) in the outstanding Office Action. Clearly, these compounds disclosed by Suzuki et al stand for nothing more than supporting the notion that modification of the number of methylene groups in the linker between the amido group and the piperidinyl ring would be within the general capabilities of the artisan. However, it is well settled that

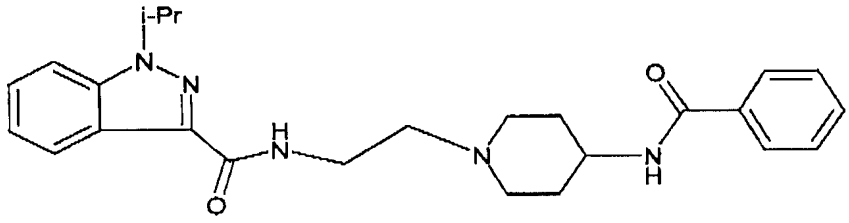
whether the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness (MPEP §2143.01). Indeed, the mere fact that the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). Indeed, absent Applicants' disclosure to serve as the guidepost, no objective reason to combine the teachings in a way that would place the artisan in possession of the claimed invention can be found.

With respect to difference (ii), the Examiner again does not address the previous arguments. Specifically, Applicants argued that Schaus et al do not disclose or suggest that the rotation of the piperidinyl ring is an optional choice. In particular, it is not true that compound 19j and compound 23j are described in Schaus et al as having both "potent binding activity" as stated by the Examiner. Schaus et al literally define only compound 19j a "potent 5-HT4 receptor antagonist" (see page 1948 right column last four lines) while compound 23j is only mentioned as a "5-HT4 receptor antagonist" without the adjective "potent" (see page 1951 left column, 2nd paragraph, last nine lines). As a consequence, the rotation of the piperidinyl ring may influence the activity.

Applicant further submit that a comparison of compound 19j with compound 23j is not an objective comparison for arguing that the rotation of the piperidinyl ring is an optional choice, because compounds 19j and 23j have other structural differences that can influence their activity, as shown below:



19j



23j

In particular, compound 19j has no methylene groups linking the indazolamido ring to the piperidinyl ring, while has two methylene groups linking the piperidinyl ring to the benzamido ring. On the contrary compound 23j has two methylene groups linking the indazolamido ring to the piperidinyl ring, while has no methylene groups linking the piperidinyl ring to the benzamido ring.

In view of the foregoing, Applicants submit that the present invention is not obvious in view of Catlow et al, even when combined with Suzuki et al and Schaus et al, as this reference fails to provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds. Thus, Catlow et al, even when combined with Suzuki et al and Schaus et al, fails to support even a *prima facie* case of obviousness.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon

Vincent K. Shier, Ph.D.
Registration No. 50,552

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)